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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KATHERINE GORDON

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GTC BIOTHERAPEUTICS, INC.

C/O WOLF, GREENFIELD & SACKS, P.C.

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BOSTON, MA 02210-2206

EXAMINER

MONTANARI, DAVID A

ART UNIT

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1632

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 07/839,194	Applicant(s) GORDON ET AL.	
	Examiner DAVID MONTANARI	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 June 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,5-8,11,16,17 and 30-33 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,5-8,11,16,17 and 30-33 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicants arguments and amendments filed on 6/3/2008 are entered.
2. The Final Rejection mailed on 5/3/2007 is withdrawn. Prosecution in the instant case is therefore reopened.
3. The declaration by Harry M. Meade has been considered and found persuasive.
4. Claims 30-33 are new.
5. The 35 USC 102(b) rejection is withdrawn in view of Applicant's arguments.
6. Claims 1, 2, 5-8, 11, 16, 17 and 30-33 are examined in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicants in their amendment have added new claim 31, which is drawn to a milk serum protein promoter wherein said promoter is an alpha-lactalbumin promoter.

Regarding claim 31, the specification teaches on pg. 4 lines 11 and 12 that "Another example of a milk serum protein described in the literature is alpha-lactalbumin". This is the only reference in the specification that mentions "alpha-

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lactalbumin” and this is referring to the protein, not the promoter. The promoter and the protein of alpha-lactalbumin are distinct from each other. If Applicant believes this rejection is made in error they are invited to cite line and page number where support is found for an alpha-lactalbumin promoter.

Claims 1, 2, 5-8, 11, 16, 17 and 30-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification provides only a description of one mammalian serum milk protein promoter, and that is the mouse WAP promoter. The art of record (Qasba et al.) provides description of only one other milk serum protein promoter and that is the rat alpha-lactalbumin promoter, described below. There is no description of any other WAP promoter or other mammalian milk serum protein promoter such that at the time of filing, 1986, it is evident that applicant had possession for the breadth of the claimed invention. Furthermore, the disclosure does not describe mammalian serum milk promoters for their breadth such that their structure could be envisioned by the skilled artisan at the time of filing.

In addition, it is important to note that the courts have support this concept of written description. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the

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filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the mouse WAP promoter described in the instant specification the skilled artisan cannot envision the detailed chemical structure of the encompassed promoters, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it, or the mere reference to its starting material. It is noted that the specification mentions that other mammalian milk serum proteins were known in the art at the time of filing, and specifically indicates the alpha-lactalbumin protein (pg. 4, lines 11-15) and further mentions the beta-lactoglobulin promoter (pg. 15. line 5) and the casein promoter (pg. 15 lines 8-9). However, this is not seen as sufficient written description for the genus of mammalian milk protein promoters, or a reduction to practice for the promoters as only the protein is disclosed. Further the claimed invention encompasses any mammalian milk promoter sequence from any species of mammal, however the specification only teaches the mouse WAP promoter (pg. 9 line 8). It is further noted that Qasba et al. (1984, *Nature*, Vol. 308, pgs. 377-380) teach a rat alpha-lactalbumin promoter sequence fragment, however no other species of the alpha-lactalbumin promoter are described. The promoter sequence is DNA and that sequence itself is required. See *Fiefs v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

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One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the mouse WAP promoter as contained in ATCC Accession No. 67032 (pg. 10 line 17) and the rat alpha-lactalbumin promoter, meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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Claims 1, 2, 5-8, 11, 16 and 17 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,727,405 for reasons of record in the office action mailed 8/7/2006 and 5/2/2007.

Claims 1, 2, 5-8, 11, 16, 17 remain and 30-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-41 of U.S. Patent No. 7,045,676 for reasons of record in the office action mailed 8/7/2006.

Response to Arguments

Applicants argue in amendment filed 6/3/2008 that when the claims are in otherwise allowable form, Applicant will file a terminal disclaimer at that time. This is not persuasive. A statement of acquiescence over a pending rejection does not overcome the rejection and thus the double patenting rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 2, 5-8, 16, 17, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Qasba *et al.* (1984, Nature, Vol. 308, pgs. 377-380) and Bujard *et al.* (US Patent 4,495,280-Jan. 22, 1985).

Qasba *et al.* teach a DNA sequence of the rat α -lactalbumin gene comprising 1247 bases of the promoter containing a TATA box (page 379) linked to the entire coding sequence for the secreted protein lactalbumin. The specific DNA sequence identifying the 1247 base pair 5' end, a 19 amino acid secretion signal, and a lactalbumin encoding sequence is set forth in figure 1. Dependent claims set require that the DNA contain a polyadenylation signal, more specifically reciting that it is derived from SV40, which can reasonably be interpreted to be effectively any polyadenylation sequence as well as other construct elements. Qasba *et al.* teach that the DNA sequence contains a AATAAA polyadenylation sequence at the 3' end, as well as a transcriptional stop signal at position 3762 (see legend for figure 1, page 379). Qasba *et al.* do not teach a DNA construct comprising a gene under the transcriptional control of a mammalian milk protein promoter sequence which does not naturally control transcription of said gene.

However at the time of filing it was known in the art that using exogenous promoters to drive transgene expression was useful for the commercial production of naturally occurring and synthetic polypeptides. Bujard *et al.* teach that it was routine at the time of filing for constructs to comprise exogenous promoters to drive expression of transgenes of interest (col. 9 line 62 bridge col. 10 lines 1-16). Bujard *et al.* teach that "In developing a process for the commercial production of polypeptides, many factors will be involved in optimizing the economic and efficient production of the polypeptides. Included among these factors are regulatory signals, which are DNA sequences involved with the regulation of replication, transcription and translation" (col. 1 lines 18-25). Bujard continues to teach that in regard to the efficient production of polypeptides, one area of interest is at the level of transcription (col. 1 lines 1-2). Bujard continues that

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transcription involves the enzyme RNA polymerase and that RNA polymerase binds to a site called a promoter, and that it has been observed that promoters vary in their activity (col. 1 lines 25-29). Bujard continues to teach that the more active promoters are referred to as strong promoters (col. 1 lines 34-35). Bujard continues that a vector is constructed having a promoter, followed by a DNA sequence of interest, optionally followed by one or more translational stop codons in one or more reading frames, followed by a balanced terminator, followed by a marker allowing for selection of transformants (col. 2 lines 6-11). Bujard continues that the construct or regulatory portions thereof are used for efficient transcription of RNA or gene expression (col. 2 lines 19-20).

Therefore it would have been *prima facie* obvious to one having ordinary skill in the art at the time of filing to combine the teachings of Qasba et al. concerning a description and function for the rat alpha-lactalbumin promoter with the teachings of Bujard et al. concerning the importance of promoter selection in the commercial production of proteins, to develop a DNA construct which comprises a milk serum protein promoter that drives expression of a gene of interest for the commercial production of polypeptides.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

No claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is (571)272-3108. The examiner can normally be reached on M-Tr 8-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 1-571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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